Does whipworm increase the pathogenicity of *Campylobacter jejuni*? A clinical correlate of an experimental observation

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Campylobacter jejuni is a leading cause of acute diarrhea worldwide, usually mild and self-limiting. No adequate hypothesis has yet been formulated to explain why in an otherwise healthy host this infection is occasionally severe. In a pig model, *C jejuni* has been shown to be pathogenic only in the presence of swine whipworm. A human case of life-threatening *C jejuni* colitis leading to toxic megacolon and acute renal failure, associated with concomitant whipworm (*Trichuris suis*) ova in the feces, is reported. The potential of *T suis* to potentiate *C jejuni* in humans deserves further study.

Key Words: Campylobacter; *Enteric infection*; Trichuris suis; *Whipworm*

Le trichocéphale augmente-t-il la pathogénicité des bactéries *Campylobacter jejuni*? Corrélat clinique d'une observation expérimentale

Campylobacter jejuni est l'une des principales causes de diarrhée aiguë, généralement bénigne et spontanément résolutive, dans le monde. Toutefois, aucune hypothèse satisfaisante n'a été émise jusqu'à maintenant visant à expliquer pourquoi l'infection peut parfois devenir très grave chez un hôte par ailleurs en bonne santé. Dans un modèle d'étude chez le cochon, les expériences ont montré que *C jejuni* ne devenait pathogène qu'en présence du trichocéphale porcin. Voici un cas de colite à *C jejuni* chez l'homme, virtuellement mortelle, ayant abouti à un syndrome colectasique et à une insuffisance rénale aiguë, associée à la présence concomitante d'œufs de trichocéphale (*Trichuris suis*) dans les fèces. La possibilité que *T suis* accentue la pathogénicité de *C jejuni* chez l'homme mérite d'être approfondie.

CASE PRESENTATION

A previously healthy, 42-year-old black man presented to the emergency room with a one-day history of crampy suprapubic pain and watery, nonbloody diarrhea that he associated with eating a chicken dish at a local restaurant the previous day. There was nausea and vomiting, but no fever. Previous meals were home-cooked, and there was no history of alcohol, recent travel or antibiotic use, or other ill contacts. He was on no medications. He had immigrated from Somalia in the past year. Human immunodeficiency virus serostatus was negative.

Initial examination revealed an ill looking man, who was afebrile, tachycardic (125 beats/min) and dehydrated. The abdomen was diffusely tender and distended, without any peritoneal signs. Digital rectal exam revealed no masses and no blood. Abdominal radiographs and ultrasound demonstrated a dilated colon, confirmed on computed tomography, which also showed pericolic inflammatory changes around the descending colon. Initial abnormal laboratory tests included an elevated white blood cell count of 21.7×10^9/L (absolute neutrophil count of 19.35 with no eosinophilia). All other laboratory tests were normal, including a creatinine of 79 µmol/L (normal values 60 µmol/L to 120 µmol/L), platelets 324×10^9/L (normal values 140×10^9/L to 400×10^9/L), electrolytes and serum liver transaminases. He was empirically started on ciprofloxacin and metronidazole pending stool cultures.

Over the next several days in hospital, the diarrhea and vomiting improved, but his abdomen became progressively distended. The creatinine increased from 79 µmol/L on day 1 to 783 µmol/L by day 3, with oliguria. Elevations were seen in serum aspartate aminotransferase (52 U/L, normal values 7 U/L to 40 U/L) and alanine aminotransferase (126 U/L, normal values 10 U/L to 45 U/L), as well as alkaline phosphatase (166 U/L, normal values 35 U/L to 125 U/L), total bilirubin (29 µmol/L, normal values 0 µmol/L to 23 µmol/L) and lactate dehydrogenase (554 U/L, normal values 100 U/L to 195 U/L). Blood smear showed slight polychromasia but no fragmented cells. Blood cultures were negative. New joint pain and effusions developed in both knees and wrists. Repeat renal ultrasounds with Doppler ruled out any postrenal obstruction, and demonstrated adequate intrarenal flow. Hemodialysis was initiated to manage the acute renal failure of unknown etiology.

Stool cultures were positive for *Campylobacter jejuni*, sensitive to ciprofloxacin, and stool microscopy showed *Trichuris trichiura* larvae.

Limited colonoscopy to the transverse colon revealed severe diffuse mucosal ulceration (Figure 1) and a polypoid, flat, nonobstructing mass at 50 cm, presumably incidental. Two biopsies at 70 cm and 85 cm, respectively, showed focal acute ulcerated granulation tissue consistent with a severe ulcerating mucosal injury. No granulomas were seen. The 1 cm polypoid mass was a villous adenoma with high grade dysplasia. Renal

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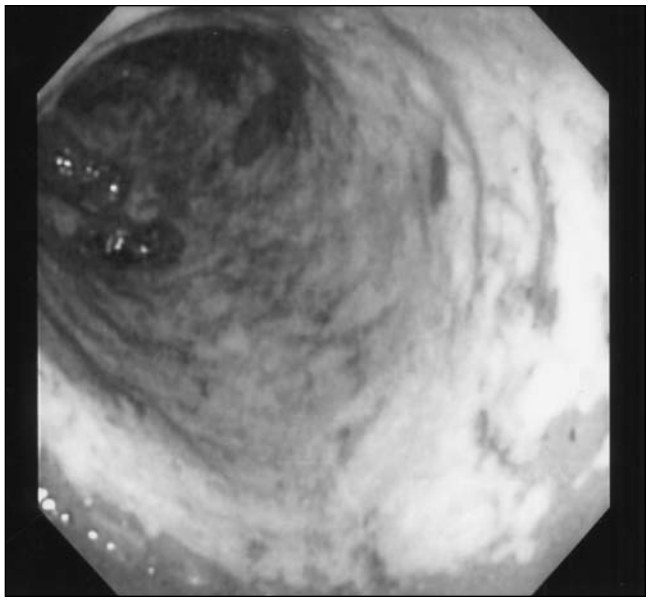

Figure 1) *Endoscopic view of transverse colon showing mucosal ulceration and denudation of mucosa*

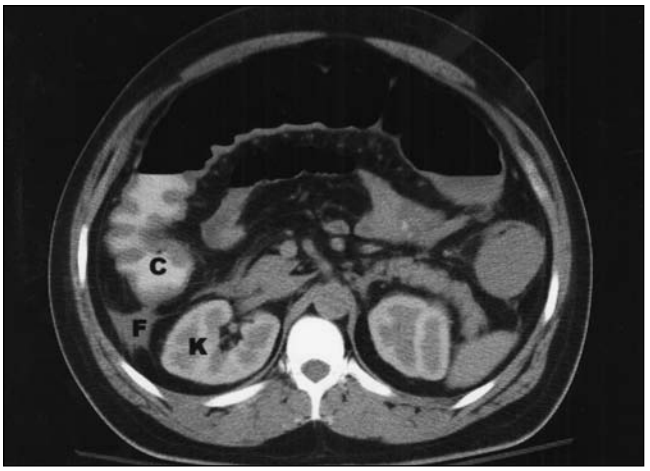

Figure 2) *Noncontrast computed tomography (CT) of the abdomen demonstrates colonic dilation and diffuse wall thickening in the ascending and transverse colon (C) consistent with colitis. Fluid (F) is present in the right paracolic gutter. Retained contrast in the kidneys (K) from previous contrast CT indicates renal failure*

biopsy showed acute tubular necrosis; on immunofluorescence mesangial deposits of immunoglobulin (Ig) A and IgM were seen with linear accentuation of the glomerular basement membrane for IgG. The exact etiology of the renal failure was unclear, although it was likely multifactorial secondary to acute tubular necrosis, and possibly IgA nephropathy.

Repeat computed tomography examination (without contrast) showed interval development of marked bowel wall thickening of the ascending and transverse colon with no change in cecal diameter. The maximum colon diameter was estimated to be 6 cm (Figure 2). A colon decompression tube was placed endoscopically into the cecum on hospital day 5 together with a nasogastric tube. The resulting colon decompression was associated with dramatic improvement in abdominal symptoms.

Over the next two weeks, the abdominal symptoms gradually resolved and renal function improved sufficiently to allow discontinuation of dialysis. The patient was discharged on hospital day 17. The *T trichiura* was then treated with mebendazole. The polypoid mass will be endoscopically resected once the renal insufficiency stabilizes.

DISCUSSION

Campylobacter infection causes an estimated 5% to 11% of infectious diarrhea in the United States (1). The vast majority of these infections result in nothing more than self-limiting diarrhea, usually watery but sometimes mixed with blood. However, in approximately 1% of cases, the campylobacter infection may become associated with complications such as life-threatening colitis, toxic megacolon, arthritis and acute renal failure (2-4), as in our patient. Other reported complications include peritonitis, visceral perforation, Guillain-Barré syndrome and IgA nephropathy (5-7). A satisfactory explanation as to why these complications develop, and why they develop so rarely, has not yet been formulated. However, in a pig model of enteric infection, *Campylobacter* does not lead to colonic infection without the concomitant presence of the swine whipworm, *Trichuris suris* (8,9). Moreover, invasion of intestinal cell cultures by *C jejuni* is dose dependent in the presence of excretory-secretory products from adult *T suris* (10). Presumably, *Trichuris* larvae attach to colonic epithelium and then release excretory-secretory products such as metalloproteases, proteases and glycoproteins (11). These compounds then induce epithelial damage, exposing the underlying fibronectin in the extracellular matrix, promoting campylobacter attachment via the CadF adhesion molecule (12). Mansfield et al (13) recently found that three-day-old germfree pigs who were given dual infections with *T suis* and *C jejuni* had more profuse diarrhea and more severe histological changes than pigs given no pathogens, only *T suis*, or only *C jejuni*. In the proximal colon where adult worms were found, there was significant hemorrhage and inflammatory cell infiltrates, and in the distal colon, there were abscessed lymphoglandular complexes with intracellular *C jejuni* (13).

There are no reported human cases examining coincident whipworm and campylobacter infection in the published English literature. However, given the evidence from animal and in vitro models, we hypothesize that our patient's whipworm infection may have predisposed him to a more severe course of *C jejuni* infection, including deep colonic ulcers, toxic megacolon and acute renal failure.

This case report is not a study of mechanism, or evidence of a causal relationship between severe *Campylobacter*-induced colitis and whipworm infection. Confirmation of our hypothesis requires further research in several areas. Our patient was infected with human *T trichiura*, which has been shown to be a distinct organism from porcine *T suis* (14, 15). Worldwide, over one billion individuals are estimated to harbour *T trichiura*, mostly in developing countries (16). Given that most individuals are asymptomatic from their whipworm infection, the potential intensity of infection and morbidity may be underestimated (17). The pathology of the intestinal lesions caused by *T trichiura* remains inadequately defined (18). However, there are studies demonstrating significant adverse consequences of *T trichiura* characterized by chronic dysentery, predisposition to rectal prolapse and anemia (19,20). In addition, *T trichiura* has

been shown to have an invasive phase during which the adult worms, their eggs or their larvae are able to elicit strong inflammatory responses, resulting in mucosal erosion and microhemorrhage. The similarity of these responses to idiopathic inflammatory bowel disease has been highlighted by several case reports (21-23). Currently, it is not known whether *T trichiura* produces secretory-excretory products similar to that of porcine *T suis* or how *T trichiura* modifies the inflammatory cytokine response. In addition, other mechanisms accounting for the severity of this patient's campylobacter infection are possible, including a microperforation associated with the dysplastic polyp seen on colonoscopy. It is unlikely that an immunocompromised state was responsible for this patient's severe colitis and associated complications, given his negative human immunodeficiency serology.

The presence of whipworm may be coincidental, but the possibility that it potentiated *C jejuni* pathogenicity is an intriguing possibility worthy of further investigation.

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